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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,815	02/27/2002	Christen Marie Anderson	660088.435C2	8204

500 7590 10/01/2003

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	12

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,815	ANDERSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-19* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 9,* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 13-19 are currently pending and are present for examination. Claims 13-16, 18-19 are now under consideration. Claim 17 remains withdrawn from consideration as being drawn to non-elected invention (i.e., non-elected species, SEQ ID NO:29).

Election/Restrictions

Applicant's election of Group III, claim 13-19 in Paper No. 11 is acknowledged. Because applicant has neither traversed nor distinctly and specifically pointed out the supposed errors in the restriction requirement, and cancelled all non-elected claims the election has been treated as an election without traverse (MPEP § 818.03(a)).

Examiner acknowledges the election of species SEQ ID NO:67 and SEQ ID NO:70 applicants. Applicants indicate that they have elected epitope tag sequence of SEQ ID NO:1 and the tat sequence of SEQ ID NO:70 for use according to the method of claim 18. Examiner has concluded that applicants are referring to the fusion protein with SEQ ID NO:71 indicated in claim 19.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 and claims 14-16, 18-19 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the phrase "effective amount of". The metes and bounds of the above phrase is not clear to the Examiner. The specification provides a definition at page 111 that effective amount is "the amount of a therapeutic agent that when administered to a subject *by* an appropriate dose and *regime* results in *desired results.*". However, such a definition is very vague and unclear. It is not clear to the Examiner as to what applicants mean by the phrases "by an appropriate dose", "and regime" in the definition. While this may be typographical errors, it is highly unclear as to what results are considered as "desired results" by the applicants. Therefore, even though applicants provide a definition for the above phrase in the claim, the definition is highly vague and indefinite.

Claim 14 and claims 15-16, 18-19 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites the phrase "selected from the group consisting of". However, the claim is silent about the group and there is no recitation of a group of compositions. Therefore, it is not clear to the Examiner as to which "group" applicants are referring to.

Claim 14 and claims 15-16, 18-19 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites the phrase "one or more activities". The metes and bounds of the word "activities" are not clear to the Examiner. It is not clear as to what specific activities of IF1, applicants are referring to in this claim. Without a reference to specific activity of IF1, the phrase renders the claim indefinite.

Claim 14 and claims 15-16, 18-19 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites the phrase "a composition that mimics IF1". The metes and bounds of the said phrase are not clear to the Examiner. It is not clear as to what applicants mean by "mimics". While the literal meaning of the above term is clear to the Examiner, the meaning of the above term in the context of the claim 14 is not clear to the Examiner.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16, 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diabetes comprising administering to a patient an empirically determined amount of a fusion polypeptide with SEQ ID NO:71 such that the symptoms or cause of the diabetes disorder (for example reduced release of insulin) is

eliminated or such that the pancreatic cells are restored to synthesize and secrete and release insulin at appropriate times, does not reasonably provide enablement for such a method using any "compound" or composition comprising any compound which simply increases the synthesis of mitochondrial ATP in any cell, or decreases the hydrolysis of mitochondrial ATP in any cell or does both in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13-16, 18 are so broad as to encompass a method of treating the diabetes disorder by administering simply "any compound" that increases the synthesis of mitochondrial ATP in any cell, or decreases the hydrolysis of mitochondrial ATP in any cell or does both in any cell. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of compounds and "any cell" broadly encompassed by the claims. Since the amino acid sequence of a protein or the chemical make-up of a compound determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of

modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the use of a single fusion protein with amino acid sequence SEQ ID NO:71. It would require undue experimentation of the skilled artisan to make and use any "compounds" as encompassed by the claims . The specification is limited to teaching the use of SEQ ID NO: 71 as the specific compound that can be used for treating diabetes, but provides no guidance with regard to the making of variants and mutants or with regard to other uses of any or all compounds. In view of the great breadth of the claim, amount of experimentation required to make the claimed compounds , the lack of guidance, working examples, and unpredictability of the art in predicting function from a primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

With reference to polypeptides and polynucleotides while recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of all or any compounds for the above method because the specification does not establish: (A) a rational and predictable scheme for treating diabetes by administering any or all compounds which modulate ATP levels in any cell; (B) a rational and predictable scheme for modifying any "compound" with an expectation of obtaining the desired biological function; (C) all or any compound(s) which affects ATP levels in any or all cells can be used for treating diabetes; (D) regions of the protein structure in IF1 which may be modified without affecting its activity; (E) the general tolerance of IF1 to modification and extent of such tolerance; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of "compounds" having the desired biological characteristics for treating diabetes is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 13-16, 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-16, 18 are directed to a method comprising the use of "compounds". Claims 13-16, 18 are rejected under this section of 35 USC 112 because the claims are directed to a method which uses a genus of "compounds" including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue that have not been disclosed in the specification. No description has been provided of the compounds encompassed by the claim. No information, beyond the characterization of SEQ ID NO:71 has been provided by applicants which would indicate that they had possession of the claimed genus of "compounds". The specification does not contain any disclosure of the structure of all the "compounds" within the scope of the claimed genus. The genus of compounds claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides and compounds are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-16, 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebowitz et al. (Arch. Biochem. Biophys., 1993, Vol. 301(1) :64-70 Ref. in IDS), Matschinsky, 1996, Diabetes, Vol. 45:223-241 Ref. in IDS) and Frankel et al. (US 5,804,604, 9-8-1998, Ref. in IDS). Claims 13-16, 18-19 in this instant application are drawn to a method of treating diabetes comprising administering to a patient in need thereof an effective amount of a compound that (a)increases the synthesis of mitochondrial ATP in cells or (b) decreases the hydrolysis of mitochondrial ATP in cells or (c) does both, wherein the composition comprises a compound that inhibits or mimics the activity of IF1, wherein said composition that mimics IF1 comprises a portion of an IF1 polypeptide comprising a polypeptide of less than 35 amino acids and at least one of an optional epitope tag, a cellular transport sequence and an organellar targeting sequence such as SEQ ID NO:71.

Lebowitz et al. teach the regulation of mitochondrial ATP synthase/ATPase complex by a functional protein inhibitor labeled as IF1. While describing the detailed structure of ATP synthase complexes comprising F_0F_1 portions, the above authors also describe the inhibitor IF_1 which is known to inhibit hydrolysis of ATP. The reference provides the entire structure of the cDNA and the amino acid structure of the polypeptide IF_1 encoded the polynucleotide.

In a review article on glucose metabolism in pancreatic ß-cells and the physiological role of these cells in glucose homeostasis, Matschinsky details the role of mitochondria, the citric acid cycle, electron transport and oxidative phosphorylation with reference to insulin release (see page 229 through 233 and figure 11). While describing the above Matschinsky teaches that the rate of ATP production has to reach a threshold before insulin release is initiated and that as supply begins to predominate, the energy potential of ATP hydrolysis, increases sharply providing the signal for insulin release. Therefore it can be agreed that common knowledge in the art indicates a requirement of high levels of ATP in ß-cells of pancreases for release of insulin and that it is the low level of ATP concentration that leads to withholding of insulin by ß-cells leading to insulin resistance or reduced levels of insulin seen in Diabetics.

Combining the teachings of the above two references, it would have been obvious to those skilled in the art, especially those involved in finding a treatment for diabetes disorder to identify the portion of IF_1 that is responsible for inhibiting ATP hydrolysis and deliver it to ß-cells of pancreas so that the hydrolysis of ATP is inhibited leading to maintainence of high levels of ATP concentration leading to the release of insulin. Combining such teachings with the methods taught by Frankel et al. regarding Tat-derived transport of polypeptides to target cells, it would have been obvious to those skilled in the art to make and use hybrid protein comprising Tat and the IF_1 fragment and deliver it to ß–cells of pancreas. One of ordinary skill in the art would have a motivation to do so as it is well known in the art that Diabetes is a highly debilitating disease without any alternative for the painful injections of insulin. One of ordinary skill in the art would have a reasonable expectation of success since Lebowitz et al. teach in

detail the properties and structure of IF_1 and Matschinsky teaches importance of ATP levels for insulin release and Frankel et al. provide methods for peptide transport or delivery.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao Ph.D.
Patent Examiner, A.U. 1652
9/29/03